EXHIBIT I

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Women and opioids: something different is happening here

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An opioid crisis is raging in the USA, spreading across Canada, and there is increased opioid prescribing and access to high potency opioids such as fentanyl in other countries.[1] Action is demanded through national initiatives and strategic plans[2] to address the underlying causes of this epidemic, implement effective treatments for opioid use disorders (OUD), and support research that will improve interventions. However, current planning overlooks gender differences in opioid use that have meaningful implications for preventing misuse and treating pain and OUD.

The pathway to opioid use for women is more likely to be through medical treatment than for men. The main reason for prescribing opioids is to treat pain, and population-based studies suggest women are at increased risk for pain and more sensitive to the aversive aspects of most painful stimuli.[3,4] When opioids were prescribed during US outpatient care visits between 1993 and 2014, women were more likely to be given prescriptions than men (54% *vs* 46%).[5] Similarly, a large study of patients with chronic pain who were prescribed opioids showed that women were over-represented (>63%), and this percentage increased with age (≥61 years) to 80%.[6] Women are also more likely than men to be prescribed opioids for chronic conditions, such as headache, that do not have data showing treatment benefit.[6] Furthermore, prescribing opioids with other medications that increase overdose risk is more common in women than men. For example, benzodiazepine co-prescribing, which increased each year from 2002 to 2014 in the USA, was more common for women than men (eg, 11% *vs* 7·7% in 2014).[7] Although there are more prescription opioid-related deaths among men than among women in the USA, the rate of increase in deaths is higher in women than men. Between 1999 and 2016, such deaths rose by 404% in men and 583% in women.[8]

There are other concerns about opioid prescribing practices in women. Substance use treatment admissions in the USA between 1992 and 2012 show that the percentage of pregnant women with OUD due to prescription opioids increased from 2% to 28%.[9] This increase raises concerns for maternal and newborn health, including neonatal abstinence syndrome.[10] Moreover, the pharmacological effects of opioids can differ in men and women depending upon, for example, the specific opioid and its attendant receptor subtype, dose, and active gonadal hormones.[11] Yet elucidating the effect of gender on opioid analgesia and tolerance yields mixed research results due to gender-based factors that affect the experience of pain, ranging from sex-specific molecular and hormonal interactions of particular opioids to the influence of psychosocial contexts.[3]

In addition, there is a different clinical picture for women and men in relation to use of prescription opioids. For example, women with OUD are more likely than men to report use for coping with negative emotions and pain, according to findings from a large, multisite clinical trial.[12] Although 12-month prevalence rates of OUD in the USA from 2015 are lower for women than men (1·4% *vs* 2·9%),[13] after exposure to an addictive substance, progression to substance use disorders is more rapid in women than men.[14,15] Women receiving OUD treatment due to prescription opioids also have greater functional impairment than men,[12,16] which has implications for maintaining employment, housing, relationships, and personal care. Women receiving OUD treatment are less likely than men to have been involved in the criminal justice system but are more likely to be unemployed and concerned about intimate partner violence and child care

during treatment.[17] As most family caregivers are women, OUD in women affects the wellbeing of children and families. Rates of co-occurring psychiatric disorders also vary by gender. A meta-analysis of methadone treatment for OUD showed men more likely to report alcohol use than women,[17] whereas other studies showed women have higher prevalence of any co-morbid mood disorder and anxiety disorder than men.[18]

Treatment of OUD similarly requires consideration of gender-specific approaches. Substance use interventions historically developed around the treatment of men and services often focus preferentially on the concerns of men. Women can also experience greater stigma when identified with a substance use disorder.[15,19] Consequently, women are less likely than men to enter traditional substance use treatment programmes.[15,19] Women-only programmes seem to reduce barriers to treatment entry, and women-centred services that encompass child care and domestic counselling show improved engagement and can result in better outcomes for women.[15,20]

Gender also needs to be considered in addiction pharmacotherapies. Some treatments are not as effective in women as men, such as disulfiram in cocaine use disorder,[21] whereas others are more effective in women than men, such as naltrexone for alcohol use disorder. For OUD, buprenorphine is at least as effective for women as men, although variants in the *OPRD1* gene can result in either better or worse outcomes in women.[22]

Historically, the influence of gender has been overlooked in responding to many medical conditions, including cardiovascular disease and brain disorders such as Alzheimer's disease. A failure to focus on women in the opioid epidemic can result in serious misjudgments—a 2016 study showed that among opioid overdose decedents women were three times less likely than men to receive naloxone through emergency medical services.[23]

The influence of gender differences in pain, opioid use, and OUD must be part of the response to the opioid crisis. Examples of steps to be taken for prevention and treatment in women include increasing insurance for non-opioid pain management,[2] ensuring treatment of OUD is integrated with women's needs (eg, child care, relationship counselling, screening for depressed mood and anxiety),[18,20] and enacting protection for women with children and for pregnant women so that they can seek treatment without fear of child custody loss.[10,20] Research opportunities include determining how gender differences affect pain, how best to tailor medication treatment and counselling, and how controlled substances affect neurobiological pathways resulting in specific consequences for women (eg, more rapid addiction, motivation to reduce negative emotion). Interdisciplinary studies alerting us to gender-specific psychosocial experiences that incur particular risk for women (eg, early trauma) in the context of a high stress burden (eg, sole family caregiver) are other examples of vitally needed information. Halting the momentum and effectively managing the sequelae of this opioid epidemic requires research, clinical, and policy commitments to understanding the influence of gender.

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Retraction—Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study

Following our Expression of Concern[1] we have now received further information about the conduct of the study by Philipp Jungebluth and colleagues.[2] In letters to *The Lancet*, the President of the Karolinska Institute has sent the results and conclusions of the final investigation that has identified serious flaws in the conduct and reporting of this study. The report concludes there was scientific and ethical misconduct and requests retraction of the paper. *The Lancet* is therefore retracting this research article from the scientific record.

The Lancet Editors
The Lancet, London EC2Y 5AS, UK

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1 The *Lancet* Editors. Expression of concern—Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. *Lancet* 2016; **387:** 1359.

2 Jungebluth P, Alici E, Baiguera S, et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. *Lancet* 2011; **378:** 1997–2004.

Retraction—Engineered whole organs and complex tissues

In letters to *The Lancet*, the President of the Karolinska Institute has sent the results and conclusions of the final investigation that has identified serious flaws in the conduct and reporting of the study by Philipp Jungebluth and colleagues.[1] The report concludes that part of the series paper by Stephen Badylak and colleagues[2] referring to the Jungebluth and colleagues' research article is therefore misleading. In accordance with a request from the Karolinska Institute, *The Lancet* is retracting the series paper from the scientific record.

The Lancet Editors
The Lancet, London EC2Y 5AS, UK

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1 Jungebluth P, Alici E, Baiguera S, et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. *Lancet* 2011; **378:** 1997–2004.

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The Wakley Prize Essay 2018: open for submissions

"Reading maketh a full man, conference a ready man, and writing an exact man", wrote Renaissance philosopher, scientist, and essayist Francis Bacon. *Lancet* readers might suggest a few updates to the language: "makes" for "maketh", "person" for "man", and "discussion" for "conference". But Bacon's method has stood the test of time. To be a complete physician—and a complete person—one must read, listen, and communicate. The essay, as a product of intellectual processes and personal feelings, is perhaps the best expression of Bacon's ideal.

Essays inform, engage, and entertain readers. Good essays are always truthful, always unexpected. They shake up perceptions and open up possibilities. The discursive, digressive, and intimate form of the essay